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Familial DiGeorge/Velocardiofacial Syndrome With Deletions of Chromosome Area22q11.2: Report of Five Families With a Review of the Literature

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The DiGeorge (DG), velocardiofacial (VCF), and conotruncal anomaly-face (CTAF) syndromes were originally described as distinct disorders, although overlapping phenotypes have been recognized. It is now clear that all three syndromes result from apparently similar or identical 22q11.2 deletions, suggesting that they represent phenotypic variability of a single genetic syndrome. We report on 12 individuals in five families with del(22)(q11.2) by fluorescent in situ hybridization, and define the frequency of phenotypic abnormalities in those cases and in 70 individuals from 27 del(22)(q11.2) families from the literature. Common manifestations include mental impairment (97%), abnormal face (93%), cardiac malformations (68%), thymic (64%) and parathyroid (63%) abnormalities, and cleft palate or velopharyngeal insufficiency (48%). Familial DG, VCF, and CTAF syndromes due to del(22)(q11.2) show significant inter- and intrafamilial clinical variability consistent with the hypothesis that a single gene or group of tightly linked genes is the common cause of these syndromes. Up to 25% of 22q deletions are inherited, indicating that parents of affected children warrant molecular cytogenetic evaluation. We propose use of the compound term "DiGeorge/velocardiofacial (DG/VCF) syndrome" in referring to this condition, as it calls attention to the phenotypic spectrum using historically familiar names. © 1996 Wiley-Liss, Inc.

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INTRODUCTION

DiGeorge (DG) syndrome is a developmental field defect characterized by absent or hypoplastic thymus and parathyroid glands, and conotruncal cardiac malformations [DiGeorge, 1965]. The velocardiofacial (VCF) syndrome is a multiple malformation syndrome of velopharyngeal insufficiency or cleft palate, conotruncal cardiac anomalies, typical facial anomalies, and learning disabilities [Shprintzen et al., 1981]. While these two syndromes were initially thought to be separate clinical entities, phenotypic overlap led some investigators to speculate that they share a common cause [Goldberg et al., 1985; Stevens et al., 1990]. Monosomy for chromosome 22q11 was recognized cytogenetically in a few individuals with DG syndrome [de la Chapelle et al., 1981; Greenberg et al., 1988], followed by the molecular identification of microdeletions of 22q11 in DG syndrome patients with apparently normal karyotypes [Scambler et al., 1991]. Subsequent studies of VCF syndrome patients using the same DNA probes demonstrated microdeletions in most cases [Scambler et al., 1992; Driscoll et al., 1992b; Goldberg et al., 1993]. Recently, 22q11.2 deletions have also been identified in patients with the conotruncal anomalies face (CTAF) syndrome which has conotruncal cardiac defects, an abnormal face and developmental delays [Kinouchi et al., 1976; Burn et al., 1993]. The segment of 22q11.2 involved in the cause of the DG, VCF and CTAF syndromes has been designated the "DiGeorge Critical Region," or DGCR, and spans several megabases of DNA [Scambler et al., 1991; Driscoll et al., 1992a,b]. No correlation between deletion size and phenotype is apparent [Motzkin et al., 1993; Morrow et al., 1995], suggesting that the phenotypic spectrum of DGCR deletions is the result of deletion of a single gene or tightly linked group of genes and does not represent a contiguous gene deletion syndrome [Schmickel, 1986].

Familial cases of DG, VCF, and CTAF syndromes, with apparent autosomal dominant inheritance, have been reported [Young et al., 1980; Wilson et al., 1991, 1992, 1993; Driscoll et al., 1992b, 1993]. In several, a microdeletion within the DGCR was documented in parent and offspring, both of whom exhibited abnormal phenotypes. Recent reports indicate a relatively high frequency of familial transmission of 22q11.2 microdeletions, with the affected parent often demonstrating a milder phenotype [Wilson et al., 1993; Raynan et al., 1994]. We describe 12 individuals in five families (Fig. 1) each of whom has a deletion within 22q11.2, identified by fluorescence in situ hybridization using the DiGeorge Chromosome Region probe (D22S75; Oncor, Inc., Gaithersburg, MD). We review an additional 70 deletion postive individuals from 27 families reported in the literature [Rohn et al., 1984; Keppen et al., 1988; Wilson et al., 1991, 1992; Driscoll et al., 1992b, 1993; Desmaze et al., 1993; Kelly et al., 1993; McLean et al., 1993; Holder et al., 1993; Hajianpour et al., 1994; Puder et al., 1994; Piussan et al., 1994; Lindsay et al., 1995a,b].

CLINICAL REPORTS

Family 1

The propositus (II-1) is a 6-year-old boy who was the 3.5 kg product of a term gestation to a 20-year-old, gravida 1, mother and 24-year-old father. Pregnancy was complicated by gestational diabetes and polyhydramnios. Shortly after birth he was found to have an interrupted aortic arch, ventricular septal defect (VSD), hypocalcemia, and absent thymus. Subsequently he manifested mental retardation and velopharyngeal insufficiency. At age 6 years, height was 121 cm (75th centile), weight was 20 kg. (50th centile), and head circumference was (OFC) 52 cm (50th centile) and he had "dysplastic" ears, lateral displacement of the inner canthi, a long prominent nose with bulbous tip, a midsternal scar from previous cardiac surgery, and long tapered fingers.

The father (I-1) is a 30-year-old man who was the 3.1 kg product of a term pregnancy complicated by rubella exposure for which the mother received gamma globulin. He had bilateral inguinal hernia repairs, velopharyngeal insufficiency which required a pharyngeal flap,

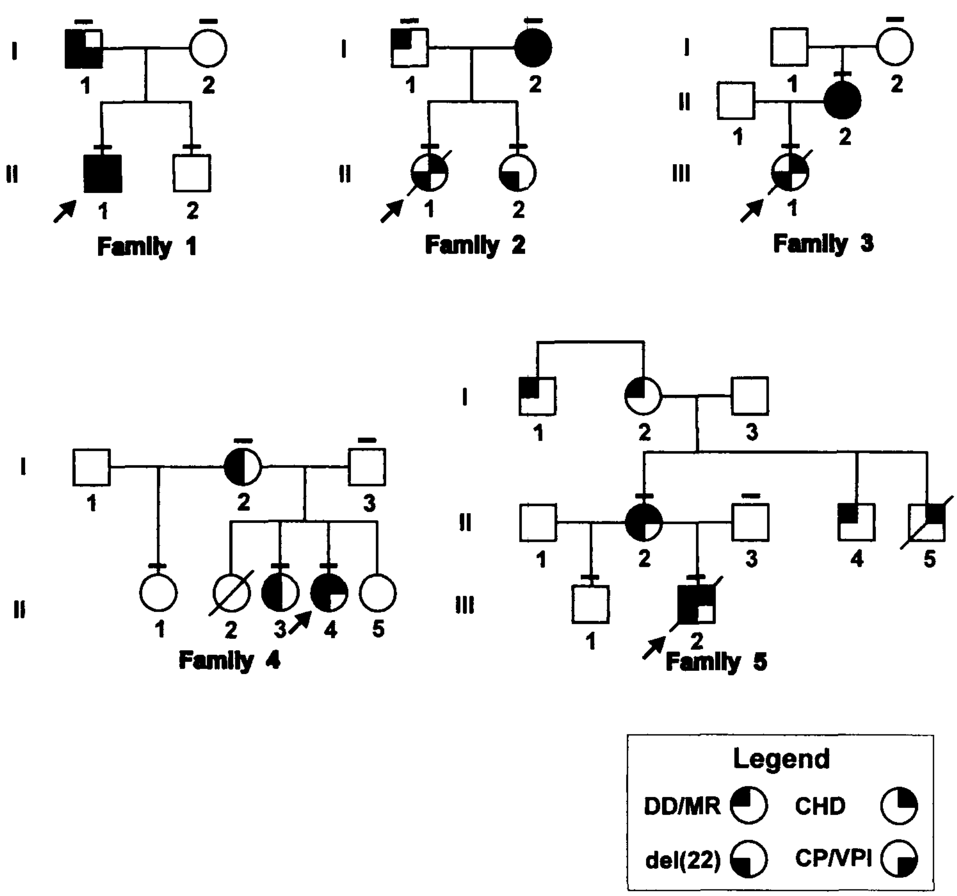

Fig 1. Pedigrees of the five families in this report coded for phenotypic features. All examined individuals [signified by a dash (—) above their pedigree symbol] have been tested for del (22)(q11.2). DD/MR, developmental delay/mental retardation; del(22), deletion of chromosome 22(q11.2) by FISH probe; CHD, congenital heart defect; CP/VPI, cleft palate/velopharyngeal insufficiency.

and developmental delays requiring special education classes. A limited physical examination shows a long face with a pear shaped nose, long tapered fingers with fingernail hypoplasia, and hypernasal speech.

Family 2

The propositus (II-1) was a 4-day-old girl who was the 3.07 kg product of a term gestation to 30-year-old, gravida 1, mother and 29-year-old father. She was diagnosed shortly after birth with a truncus arteriosus, atrial septal defect (ASD), VSD, absent thymus gland, asymptomatic hypocalcemia, and abnormal face. She had a length of 50 cm (50th centile), weight of 2.9 kg (25th centile), and had an OFC of 32.8 cm (25th centile), and also "dysplastic" ears, lateral displacement of the inner canthi, a laterally built up nose, small jaw, and long tapered fingers. She died during cardiac surgery at age 4 weeks.

A younger sib (II-2) was the 2.72 kg (25th centile) product of a 37-week gestation by dates to a 33-year-old gravida 2, para 1, mother and 32-year-old father. She had been prenatally diagnosed as having a chromosome 22q11 deletion by fluorescence in situ hybridization. In the nursery she had a poor suck requiring gavage feedings, low T-cell counts, and asymptomatic hypocalcemia. Her length was 50 cm (50th centile) and OFC was 33 cm (25th centile). Physical examination (Fig. 2a) at birth showed dysplastic ears, lateral displacement of the inner canthi, a laterally built up nose, mild micrognathia, and long tapered fingers. Echocardiogram showed normal cardiac anatomy.

The mother (I-2) is a 33-year-old woman who was the 2.9 kg product of a term pregnancy to a 19-year-old, gravida 1, mother. As an infant she had a VSD that closed spontaneously. During childhood, she had delayed development and was in special education classes with an I.Q. of 63. Mild velopharyngeal insufficiency noted at age 6 years improved spontaneously. Limited physical examination (Fig. 2b) shows large ears, lateral displacement of the inner canthi, and a long pear-shaped nose. She has limited cognitive abilities.

Family 3

The propositus (III-1) was a 6-week-old female infant who was the 2.8 kg product of a term pregnancy to a 25-year-old, gravida 1, mother. In the newborn period she was found to have an interrupted aortic arch, hypoplastic left heart, duodenal malrotation, low T-cell counts, and asymptomatic hypocalcemia. At age 6 weeks she had a length of 48.2 cm (5th centile), weighed 3.1 kg. (5th centile), and had an OFC of 35 cm (5th centile). Physical examination showed lateral displacement of the inner canthi, a laterally built up nose, micrognathia, a prominent cardiac murmur, a midsternal scar, and long tapered fingers. She died of heart failure at age 5 months.

The mother (II-2) is a 25-year-old woman who was the 2.9 kg product of a term pregnancy. During childhood she was followed for a bicuspid aortic valve, velopharyngeal insufficiency and learning disabilities requiring special education classes. Limited physical examination shows a long face, large ears, lateral displacement of the inner canthi, and a prominent pear shaped nose. She has limited cognitive abilities.

Family 4

The propositus (II-4) is a 3½-year-old girl who was the 2.3 kg (50th centile) product of a 34 week gestation

Fig 2. Typical facial appearance of patients with del(22)(q11.2). **a:** Patient II-2 from Family 2 at age 1 month. **b:** Mother (I-2) of patient II-2 from Family 2 at age 33 years. **c:** Patient II-3 of Family 4 at age 5 years. Patient ahown in a and c were only ascertained because of severely affected sibs and otherwise might never have been recognized.

TABLE I. Phenotypic Findings in Familial Cases of del(22)(q11.2)*

Report	Patient	CHD	Thymic abnormality	Parathyroid abnormality	CP/ VPI	DD/ MR	Unusual Face
Rohn et al., 1984[a]	Father	−	+	+	NT	NT	+
	Son	TA, VSD	+	+	NT	NT[b]	+
	Son	TA, VSD	+	+	+	NT	+
Keppen et al., 1988[a]	Father	RAA	+	+	+	NT	+
	Daughter	IAA, PDA, AS	+	+	−	NT[b]	+
Wilson et al., 1991	Mother	−	NT	NT	−	NT	+
	Daughter	IAA, VSD	+	+	−	NT	+
	Son	VSD	−	−	−	NT	+
	Son	CoA, PDA	−	+	−	NT	+
Driscoll et al., 1992b	Mother	VSD	NT	NT	+	+	+
	Daughter	PDA	NT	NT	+	+	+
	Mother	−	NT	NT	+	+	+
	Daughter	−	NT	NT	+	+	+
Wilson et al., 1992	Mother	TOF	NT	NT	NT	NT	NT
	Son	PA, VSD	NT	NT	NT	NT	NT
	Mother	PDA, RAA	NT	NT	NT	NT	NT
	Daughter	TA	NT	+	NT	NT[b]	NT
	Son	PA, VSD	NT	NT	NT	NT	NT
	Mother	CHD	NT	NT	NT	NT	NT
	Daughter	PA, VSD	NT	NT	NT	NT	NT
	Father	VSD, RAA, AnLSA	NT	NT	NT	NT	NT
	Daughter	VSD, AbPV, Dex	NT	NT	NT	NT[b]	NT
	Son	TOF	NT	NT	NT	NT[c]	NT
	Daughter	TOF	NT	NT	NT	NT	NT
	Father	−	NT	NT	NT	NT	NT
	Son	PDA	NT	+	NT	+	NT
	Daughter	IAA, VSD, AnRSA	+	NT	NT	NT	NT
	Son	TOF	NT	NT	NT	NT	NT
Desmaze et al., 1993	Mother	−	NT	+	−	+	+
	Son	IAA	+	+	−	NT[b]	NT
	Daughter	−	+	+	−	+	+
	Mother	−	NT	NT	−	+	+
	Daughter	IAA	+	+	−	+	+
	Son	IAA	+	NT	−	NT	NT
	Father	−	−	+	−	−	+
	Son	AbAA	−	−	−	+	+
	Son	VSD, PA	−	−	+	+	+
	Mother	−	NT	NT	+	NT	+
	Son	PA, VSD	+	NT	−	NT[c]	+
	Daughter	TA, VSD	+	NT	−	NT[c]	+
Kelly et al., 1993	Mother	−	NT	−	+	NT	NT
	Daughter	ASD, VSD	NT	−	−	NT	NT
McLean et al., 1993	Mother	−	NT	NT	+	+	+
	Son	TOF	+	+	−	+	+
Holder et al., 1993	Mother	CHD	NT	NT	+	+	+
	Daughter	−	NT	NT	−	+	+
Driscoll et al., 1993	Father	−	NT	NT	−	+	−
	Son	CHD	NT	NT	+	+	+
	Father	−	NT	NT	−	+	−
	Son	CHD	NT	NT	+	+	+
	Son	CHD	NT	NT	+	+	+
	Mother	−	NT	NT	−	+	−
	Son	CHD	NT	NT	+	+	+
	Mother	−	NT	NT	+	+	−
	Son	CHD	NT	NT	+	+	+
	Mother	−	NT	NT	+	+	+
	Son	CHD	NT	NT	−	++	
Puder et al., 1994	Mother	CHD	NT	NT	−	NT	−
	Daughter	ASD, VSD, IAA, PDA	+	NT	NT	NT	NT
Piussan et al., 1994	Mother	NT	NT	−	NT	+	+
	Daughter	NT	NT	+	NT	+	+
	Daughter	PVS	NT	+	NT	+	+

(continued)

TABLE I. *(continued)*

Report	Patient	CHD	Thymic abnormality	Parathyroid abnormality	CP/VPI	DD/MR	Unusual Face
Hajianpour et al., 1994	Mother	–	NT	–	–	+	–
	Daughter	–	NT	–	NT	+	+
	Daughter	CHD	NT	+	NT	NT	+
Lindsay et al., 1995a	Mother	VSD	–	–	+	+	+
	Child	TOF	–	–	–	NT	+
Lindsay et al., 1995b	Father	–	NT	NT	NT	NT	+
	Son	IAA, VSD, ASD, PDA	NT	NT	+	NT	+
	Daughter	–	NT	NT	+	NT	+
Current report	Father	–	–	–	+	+	+
	Son	IAA, VSD	+	+	+	+	+
	Mother	VSD	–	NT	–	+	+
	Daughter	TA	+	–	–	NT[b]	+
	Daughter	–	–	+	–	NT	+
	Mother	BiAV	NT	NT	+	+	+
	Daughter	IAA	NT	+	–	NT[b]	+
	Mother	NT	NT	NT	–	+	+
	Daughter	PDA, ASD, RAA	NT	NT	–	+	+
	Daughter	–	NT	NT	–	+	+
	Mother	TOF	NT	+	–	+	+
	Son	TOF	+	–	–	+[c]	+

* "+", Feature present; "–", Feature absent; NT, Not tested or described. AbAA, abnormal aortic arch; AbPV, absent pulmonary valve; AnLSA, anomalous left subclavian artery; AnRSA, anomalous right subclavian artery; AS, aortic stenosis; ASD, atrial septal defect; BiAV, bicuspid aortic valve; CHD, congenital heart defect; CoA, coarctation of the aorta; CP, cleft palate; Dex, dextrocardia; IAA, interrupted aortic arch; DD, disability; MR, mental retardation; NT, not tested; PA, pulmonary atresia; PDA, patent ductus arteriosis; PVS, pulmonary valve stenosis; RAA, right aortic arch; TA, truncus arteriosis; TOF, tetralogy of Fallot; VPI, velopharyngeal insufficiency; VSD, ventral septal defect.
[a] Molecular deletion confirmed in these families by Scambler et al. [1991].
[b] Patient died within the first year.
[c] Patient died in childhood.

to a 20-year-old, gravida 4, para 3, abortion 1, mother and 27-year-old father. She has an ASD, patent ductus arteriosis (PDA), right-sided aortic arch, pulmonary artery hypoplasia, abnormal face, and developmental delays. She is 89 cm tall (<5th centile), weighs 14.1 kg (25th centile), and has an OFC of 49.5 cm (50th centile). Physical examination shows overfolded "dysplastic" ears, lateral displacement of the inner canthi, prominent nasal bridge and bulbous nasal tip, a high arched palate with mild micrognathia, and long tapered fingers.

A 5-year-old sister (II-3) was the 2.8 kg product of a term pregnancy to a 19-year-old, gravida 3, abortion 1, mother and suffered from development delays ascribed to maternal neglect. She is 107 cm (25th centile) tall, weighs 18.2 kg (50th centile), and has an OFC of 49 cm (25th centile). Physical examination (Fig. 2c) shows a long face, prominent thin nose with bulbous nasal tip, apparent high arched palate, and long tapered fingers.

The mother (I-2) is a 23-year-old mentally retarded woman, who says she has fetal alcohol syndrome and knows little of her early medical history. She reported no history of having a cardiac murmur or any palatal problems. Limited physical examination shows lateral displacement of the inner canthi, a long prominent nose with bulbous nasal tip, and long fingers.

FAMILY 5

The propositus (III-2) was a 20-month-old boy who was the 1.75-kg product of a 32-week gestation to a 20-year-old, gravida 1, mother and 25-year-old father. Shortly after birth he was found to have tetralogy of Fallot, absent thymus gland, an abnormal face and homocystinuria. He was severely developmentally delayed and could not stand at 20 months. He had a length of 74 cm (<5th centile), weight of 7.7 kg (<5th centile) and OFC of 46 cm (5th centile). Physical examination showed a small chronically ill appearing boy with lateral displacement of the inner canthi, a laterally built up nose, mild micrognathia, a 3/6 systolic murmur with midsternal surgical scar and long fingers. He died at age 2 years from chronic lung disease and congestive heart failure.

His mother (II-2) is a 22-year-old mentally retarded woman who was the 2.2 kg product of a 35-week gestation to a 29-year-old, gravida 2, abortion 1, mentally retarded woman. At birth she was found to have neonatal hypocalcemia, an absent thymus gland, tetralogy of Fallot, micrognathia, and a high arched palate. Limited physical examination shows a prominent nose with a bulbous nasal tip, lateral displacement of the inner canthi, apparent high arched palate, and long fingers.

DISCUSSION

Table I contains phenotypic information on 82 deletion-positive individuals from 32 families, including the 5 families (12 individuals) from the present report. A summary of manifestations of these del(22)(q11.2) individuals is presented in Table II. The presence of DG, VCF, and/or CTAF syndrome phenotypes within the same family strongly supports a common cause of these syndromes.

It has been noted that carrier parents frequently appear to be more mildly affected than their children

[Wilson et al., 1993]. In the 32 families reviewed here, there is a much higher incidence of CHD in affected children (86%) compared to their affected parents (40%), while the occurrence of CP or VPI is more frequent in parents (52%) than their affected children (36%). These differences are most likely due to a combination of factors including 1) reproductive selection, since individuals with severe CHD are less likely to survive to adulthood and reproduce; and 2) ascertainment bias, since velopharyngeal insufficiency is more readily diagnosed in older children or adults, as compared to infants. It is also likely that many mildly affected del(22)(q11.2) individuals remain undiagnosed until a more severely affected child prompts examination of the parents. In our series, three individuals (Family 2, II-2; Family 4, I-2, II-3) presented with mild phenotypes, characterized by subtle facial changes with learning disabilities or mild mental retardation, that would have gone undiagnosed if not for a more severely affected relative. Therefore, it is difficult to draw meaningful conclusions from comparisons of parental and offspring phenotypes, as mildly affected parents with mildly affected children may remain unascertained.

While exact breakpoints have not yet been identified in DGCR deletions, it is presumed that members of the same family carry identical deletions. However, the suggestion that an unstable or expanding mutation may be responsible for intrafamilial phenotypic differences has been proposed [Wilson et al., 1992; Driscoll et al., 1993]. Recent studies, including the cloning of a translocation breakpoint within the DGCR leading to DG and VCF syndrome phenotypes, suggest that a single gene or a small number of genes are responsible for the phenotypic abnormalities seen in del(22)(q11.2) patients [Demczuk et al., 1995a; Budarf et al., 1995]. However, the possibility that there may be intrafamilial variability in deletion size warrants further investigation.

High Frequency of Familial Cases

While familial occurrence of other microdeletion syndromes is uncommon, there is a relatively high frequency of parent-to-child transmission of 22q11.2 deletions. Driscoll et al. [1992b] identified familial deletions in 2/12 (17%) VCF syndrome cases, while Wilson et al. [1993] reported parental deletions in 4/15 DG syndrome cases (27%). Matsuoka et al. [1994] found familial deletions in 5/26 CTAF cases (19%), but the actual figure may be higher, as only mothers were studied in 12 of the 26 cases. Raynan et al. [1994] found 2/11 parents deleted (18%) in their series. In our series, 5/8 del(22)(q11.2) cases were familial (63%). In summary, an average of 25% (18/72) of deletions were familial. More complete studies with a larger series of cases are necessary to confirm this figure, as some parents may have been selected for study based on the presence of phenotypic abnormalities. However, in light of these findings, it appears that all parents of individuals with 22q11.2 deletions should be evaluated, since recurrence risks are greatly altered if a familial deletion is detected.

Maternal Transmission of del(22)(q11.2)

Preferential maternal transmission of 22q11.2 deletions has been noted by several investigators [Shprintzen et al., 1981; Wilson et al, 1993; Desmaze et al., 1993]. Of 42 deletion-positive families reported to date, 32 have demonstrated inheritance through the mother [Rohn et al., 1984; Keppen et al., 1988; Wilson et al., 1991, 1992, 1993; Driscoll et al., 1992b, 1993; Desmaze et al., 1993; Kelly et al., 1993; McLean et al., 1993; Holder et al., 1993; Hajianpour et al., 1994; Puder et al., 1994; Piussan et al., 1994; Raynan et al., 1994; Matsuoka et al., 1994; Lindsay et al., 1995a,b; present report]. Demczuk et al. 1995b] presented hypotheses to explain this finding, including (1) decreased reproductive success or fertility of male deletion carriers, or (2) differential expression of genes dependent on parental origin (i.e., imprinting), such that children of male deletion carriers are more or less severely affected than offspring of maternal carriers, and thus not ascertained. Complete sibship data, available for 21 families presented in this review, indicates that male deletion carriers do not exhibit reduced fertility when compared to female deletion carriers, as the 5 fathers had 17 children (3.4 children/father), while the 16 mothers had 34 children (2.1 children/mother). The sex ratio of offspring (25 males:24 females) together with the sex ratio of reported neonatal or childhood deaths (5 males:7 females) suggests that phenotypic severity is comparable for both sexes. Furthermore, deletion-positive fathers were just as likely to have a child with a lethal phenotype as deletion-positive mothers, in that 4/17 paternal offspring (24%) died as compared to 8/33 maternal offspring

TABLE II. Summary of Clinical Findings in del(22)(q11.2) Patients*

Clinical Abnormality	Current report 5 families (N = 12)	%	Literature cases 27 families (N = 70)	%	Total 32 families (N = 82)	%	Affected parents (N = 32)	%	Affected children (N = 50)	%
Cardiac defect	8/11	73	46/68	68	54/79	68	12/30	40	42/49	86
Unusual face	12/12	100	44/50	88	56/62	90	20/26	77	36/36	100
Thymic abnormality[a]	3/6	50	15/22	68	18/28	64	2/6	33	16/22	73
Parathyroid abnormality[b]	4/7	57	18/28	64	22/35	63	5/10	50	17/25	68
Cleft palate/VPI	3/6	50	21/46	46	24/57	42	12/23	52	12/33	36
DD/MR	9/9	100	32/33	97	41/42	98	19/20	95	22/22	100

* VPI, velopharyngeal insufficiency; DD, developmental disability; MR, mental retardation.
[a] Includes thymic aplasia or hypoplasia, or abnormal T cell counts.
[b] Includes parathyroid aplasia or hypoplasia, or hypocalcemia.

(24%). These data suggest that imprinting does not play a role in the phenotypic variability seen in 22q11.2 deletions. Reports of normal individuals with uniparental disomy for chromosome 22 further support the absence of imprinted genes on chromosome 22 [Palmer et al., 1980; Schinzel et al., 1994].

Another hypothesis is that a female deletion carrier may be more likely to transmit the deleted allele to her children (sex-specific "meiotic drive"). Chromosomal meiotic drive, where one chromosome has a replication or orientation advantage on the meiotic spindle over its homolog, occurs preferentially in females [Lyttle, 1993]. However, more likely is that the higher frequency of maternally-transmitted deletions reflects a bias in ascertainment, as mothers may be more likely to accompany their children to clinic visits, and thus be tested if subtle phenotypic changes are noted. Four of five maternal deletions identified by Matsuoka et al. [1994] were from a series of 12 cases where only mothers were studied. More complete ascertainment of families is necessary to determine the basis of the observed excess of maternally-inherited DGCR deletions.

Nosology

To call attention to the shared etiology of DG, VCF, and CTAF syndromes due to deletions of chromosome 22, Wilson et al. [1993] proposed the use of the acronym CATCH 22 (**C**ardiac abnormalities, **A**bnormal facies, **T**hymic hypoplasia, **C**left palate, **H**ypocalcemia, and deleted chromosome **22**). However, this term has negative connotations [Heller, 1962], and as such we feel it is inappropriate for use when counseling family members with 22q11.2 deletions. The term "del 22q11.2 syndrome" while emotionally neutral does not confer any phenotypic information and may prove inaccurate as some individuals with this syndrome may be shown in the future to have single gene mutations. Therefore, we propose the use of the compound term "DiGeorge/velocardiofacial (DG/VCF) syndrome" in referring to this condition, as it calls attention to the phenotypic spectrum using historically familiar names.

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